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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/086,177	02/26/2002	Christopher R. Tudan	080421-000100US	1250

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TOWNSEND AND TOWNSEND AND CREW, LLP
TWO EMBARCADERO CENTER
EIGHTH FLOOR
SAN FRANCISCO, CA 94111-3834

EXAMINER	
BUNNER, BRIDGET E	
ART UNIT	PAPER NUMBER
1647	

SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	01/10/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.

Office Action Summary	Application No.	Applicant(s)	
	10/086,177	TUDAN ET AL.	
	Examiner	Art Unit	
	Bridget E. Bunner	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 October 2006*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *35* is/are allowed.

6)☒ Claim(s) *33-34* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *26 February 2002* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 16 October 2006 has been entered.

Status of Application, Amendments and/or Claims

The amendment of 16 October 2006 has been entered in full. Claims 1-32 are cancelled. Claims 33-35 are added.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claims 33-35 are under consideration in the instant application.

Withdrawn Objections and/or Rejections

1. The objection to claim 28 as set forth at pg 2 of the previous Office Action of 12 October 2005 is *withdrawn* in view of the cancelled claim (16 October 2006).

2. The rejection of claims 23 and 27-32 under 35 U.S.C. § 112, first paragraph (scope of enablement) as set forth at pg 3-7 of the previous Office Action of 12 October 2005 is *withdrawn* in view of the cancelled claims (16 October 2006).

3. The rejection of claims 23 and 27-28 under 35 U.S.C. § 112, first paragraph (written description) as set forth at pg 7-9 of the previous Office Action of 12 October 2005 is *withdrawn* in view of the cancelled claims (16 October 2006).

4. The rejection of claims 23 and 27 under 35 U.S.C. § 112, first paragraph (new matter) as set forth at pg 10-11 of the previous Office Action of 12 October 2005 is *withdrawn* in view of the cancelled claims (16 October 2006).

Claim Objections

5. Claims 33 and 34 are objected to because of the following informalities:

5a. Claim 33 uses the acronym "CXCR4" without first defining what it represents in the independent claims. While the claims can reference acronyms, the material presented by the acronym must be clearly set forth at the first use of the acronym.

5b. Claim 33 recites "SEQ ID NOS: 208" in line 4 rather than "SEQ ID NO: 208".

Appropriate correction is required.

Claim Rejections - 35 USC § 112, second paragraph

6. Claims 33-34 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

6a. Claims 33-34 are rejected as being indefinite because it is unclear whether open or closed language is intended. Claim 33 recites both "closed" (line 1, "is") and "open" (line 2, "having") transitional phrases. See MPEP § 2111.03.

Claim Rejections - 35 USC § 112, first paragraph

Scope of Enablement

7. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a CXC chemokine receptor 4 (CXCR4) agonist peptide comprising (a) an N-terminal sequence comprising amino acids 1-14 of stromal cell derived factor-1 (SDF-1);

(b) a C-terminal sequence comprising amino acid 55-67 of SDF-1 and wherein the C-termini is an acid or an amide; (c) a peptide spacer sequence linking the N-terminal sequence to the C-terminal sequence, wherein the peptide spacer sequence comprises 4 glycine residues; and optionally (d) an internal cyclic lactam bond between amino acid residues 20 and 24 in the C-terminal sequence of the peptide agonist wherein residue 24 is E or D, ***does not reasonably provide enablement*** for a CXC chemokine receptor 4 (CXCR4) agonist peptide comprising (a) a N-terminal sequence homologous to amino acids 1-14 of native SDF-1; (b) a C-terminal sequence homologous to amino acids 55-67 of native SDF-1, and (c) a spacer of the formula G_{1-4} or $(CH_2)_{1-20}$. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims. The basis for this rejection is set forth for claims 23 and 27-32 at pg 3-7 of the previous Office Action of 12 October 2005.

Applicant's arguments (16 October 2006), as they pertain to the rejection have been fully considered but are not deemed to be persuasive for the following reasons.

(i) At pg 45 of the Response of 16 October 2006, Applicant indicates that they have restricted the claim scope to the N and C termini of a preferred species and supply a Rule 132 declaration by co-inventor, Dr. Merzouk, evidencing the activity of linkers having four amino acids other than four glycines. Applicant argues that in his declaration, Dr. Merzouk presents his work with CXCR4 binding peptides having some 30 different linkers. Applicant points out that as expected, all 30 peptides exhibited activity in the CXCR4 binding assays. At the bottom of pg 46 of the Response, Applicant contends that the activity of the 30 different peptides clearly teaches that the make-up of the linkers is not critical. Applicant states that if it were critical, and

if it required significant experimentation to identify operable embodiments, the Examiner's concerns would be well taken. Applicant indicates that Dr. Merzouk's declaration clearly states that the spacer region is not critical to function beyond its ability to provide a degree of flexibility.

Applicant's arguments and the Merzouk declaration filed under 37 CFR § 1.132 on 16 October 2006 have been considered and are deemed insufficient to overcome the rejection of claim 33 based upon 35 U.S.C. § 112, first paragraph for the following reasons. In assessing the weight to be given expert testimony, the examiner may properly consider, among other things, (1) the nature of the fact sought to be established, (2) the strength of any opposing evidence, (3) the interest of the expert in the outcome of the case, and (4) the presence or absence of factual support for the expert's opinion. See Ex parte Simpson, 61 USPQ2d 1009 (BPAI 2001), Cf. Redac Int'l. Ltd. v. Lotus Development Corp., 81 F.3d 1576, 38 USPQ2d 1665 (Fed. Cir. 1996), Paragon Podiatry Lab., Inc. v. KLM Lab., Inc., 948 F.2d 1182, 25 USPQ2d 1561, (Fed. Cir. 1993). In the instant case, (1) the nature of the fact sought to be established is whether or not the length and make-up of the linker of the claimed CXCR4 agonist allows the linked N- and C-terminal SDF-1 fragments to adopt a spatial orientation similar to native SDF-1. (2) It is important to note that the instant specification only discloses activities for CXCR4 agonist peptides that contain a linker with four glycine residues (see pages pg 52, lines 1-5, 20-25; Table 2; pg 56, lines 17-22; Figure 6; pg 55, lines 1-21; Table 4; Figures 7; 59, lines 1-7; Figures 10-11). The specification does not disclose any methods or working examples regarding CXCR4 agonists with any other linkers. The Examiner previously presented evidence that the use of the four glycine linker "is to allow the N- and C-terminal fragments to adopt a spatial orientation

similar to the native protein structure" (Luo et al., pg 43, col 2). There is also strong opposing evidence showing that linkers play an essential role in maintaining domain interactions (see discussion of Ikebe et al., Nett et al., van Leeuwen et al., and Robinson et al., below in section (ii)). (3) Regarding the interest of the expert in the outcome of the case, it is noted that Dr. Merzouk is one of the inventors of the instant application. (4) Finally, Dr. Merzouk refers to data and facts. Specifically, Dr. Merzouk presents data indicating that 30 different CXCR4 agonists with linked N- and C- terminal SDF-1 domains have biological activity. However, the declaration simply demonstrates that the agonists have a variety of 4 amino acid linkers, with combinations of glycine and arginine, or glycine and lysine. There is no evidence in the declaration that linkers less than 4 amino acids or from one to twenty CH_2 provide CXCR4 agonist activity to the SDF-1 fusion protein. Finally, at pg 4 of the declaration, Dr. Merzouk concludes that based upon his experience in the field and the results presented therein, the claimed linkers of G_{1-4} or $(CH_2)_{1-20}$ function as spacers that serve the purpose of positioning the two termini for binding to CXCR4. Dr. Merzouk adds that an alkyl bridge or a glycine bridge are readily interchangeable, and while 4 angstoms of space is desired, some activity would be expected using compounds having linkers of the formula G_{1-4} or $(CH_2)_{1-20}$. Dr. Merzouk does not base his opinion on any particular facts other than his own considerable experience in the field. Affidavits or declarations are provided as evidence and must set forth facts, not merely conclusions. In re Pike and Morris, 84 USPQ 235 (CCPA 1949). While the declaration constitutes evidence that must be considered, there is also other evidence that linkers play an essential role in maintaining domain interactions and determine biological activity.

(ii) At the bottom of pg 45 and at the middle of pg 46 of the Response, Applicant argues that "quantity of experimentation" required to practice an invention is not the proper legal test for enablement. Applicant asserts that the true test is whether that work constitutes undue experimentation. Applicant submits that the Examiner has not provided any objective evidence or reasoning as to why the spacer might be a critical feature of the invention. Applicant argues that the Examiner's reliance on the Luo reference is misplaced because Luo merely states that the linker is needed. Applicant contends that Luo does not state that it has to be four glycines and no other linker.

Applicant's arguments have been fully considered but are not found to be persuasive. Specifically, relevant literature discloses that domain linkers can play an essential role in maintaining cooperative inter-domain interactions. For example, Ikebe et al. (J Biol Chem 273: 17702-17707, 1998) teach that deletion of four amino acids from the linker connecting two sub-domains of phosphorylated smooth-muscle myosin leads to the termination of its actin translocating activity (pg 17705, ΔGTDP; pg 17707). Ikebe et al. conclude that the flexed region in the central helix of myosin plays a critical role in the phosphorylation-dependent interaction between the N- and the C- terminal domains (middle of pg 17707). Furthermore, Nett et al. (Eur J Biochem 267 : 5777-5782, 2000) teach that changes in the linker length linking the catalytic domain of the Rieske iron-sulfur protein to a transmembrane anchor impair interaction of ubiquinol with the ubiquinol-oxidase site in the cytochrome bc_1 complex (pg 5777, col2 , 1st full paragraph). Specifically, Nett et al. disclose that the addition or deletion of just one amino acid in the linker lowers the ubiquinol-cytochrome c reductase activity by one half (abstract; pg 5780, col 1; Figure 3A). Additionally, Van Leeuwen et al. disclose that the length of the linker region

connecting two subdomains of Oct-1 influences the specificity and affinity of POU domain DNA binding (EMBO J 16(8): 2043-2053, 1997; pg 2044, second full paragraph through fourth full paragraph; Figure 1). Finally, Robinson et al. disclose that a critical element in efforts to construct single-chain or hybrid proteins is "the design of the peptide linkers that serve to connect different protein domains or subunits...How important is linker design in determining the propertied of single-chain proteins? Alterations in linker regions have been found to affect the stability, oligomeric state, proteolytic resistance, and solubility of single-chain proteins" (Proc Natl Acad Sci USA 95: 5929-5934, 1998; pg 5929, 1st paragraph). Robinson et al. teach that at some point, linkers must become too short to connect the subunits in the native conformation without strain and that too much linker flexibility is detrimental to single-chain protein stability (pg 5933, col 1). Thus, the state of the art at the time the invention was made, evidences that linker length is a critical feature in joining protein domains. One skilled in the art would not be able to predict the structure and function of a CXCR4 agonist peptide of SEQ ID NO: 208 with a linker containing less than 4 glycine residues or $(CH_2)_{1-20}$.

Furthermore, the Examiner's reliance on Luo et al. is not misplaced, but rather, is particularly applicable to the instant application because the instant application and Luo et al. both generate fused N-terminal and C-terminal SDF-1 peptides. Luo et al. teach that the use of the four glycine linker "is to allow the N- and C-terminal fragments to adopt a spatial orientation similar to the native protein structure" (pg 43, col 2). Although Luo et al. only disclose the utilization of a 4 glycine linker, the reference clearly indicates that the N- and C-terminal fragments of SDF-1 have to adopt a spatial orientation similar to native SDF-1. Thus, one skilled in the art would not be able to predict the structure and function of a CXCR4 agonist

peptide of SEQ ID NO: 208 with a linker containing less than 4 glycine residues or $(CH_2)_{1-20}$. A large quantity of experimentation would also be required of the skilled artisan to generate an agonist peptide of SEQ ID NO: 208 with a linker of less than 4 glycine residues or one to twenty CH_2 spacers and screen the same for activity. According to MPEP § 2164.06, "the guidance and ease in carrying out an assay to achieve the claimed objectives may be an issue to be considered in determining the quantity of experimentation needed. For example, if a very difficult and time consuming assay is needed to identify a compound within the scope of the claim, then this great quantity of experimentation should be considered in the overall analysis". Additionally, as was found in Ex parte Hitzeman, 9 USPQ2d 1821 (BPAI 1987), a single embodiment may provide broad enablement in cases involving predictable factors such as mechanical or electrical elements, but more will be required in cases that involve unpredictable factors such as most chemical reactions and physiological activity. See also In re Fisher, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970); Amgen Inc. v. Chugai Pharmaceutical Co. Ltd., 927 F.2d 1200, 1212, 18 USPQ2d 1016, 1026 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Due to the large quantity of experimentation necessary to generate the large number of derivatives recited in the claims and screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, and the state of the art which establishes the unpredictability of the effects of linkers on protein structure and function, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

New Matter

8. Claim 33 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection.

Claim 33 is directed to a CXCR4 agonist wherein the agonist is H-[Ala^{9}-Phe^{11}]-SDF-(1-14)-LINKER-cyclo(Lys^{56}-Glu^{60})-SDF-(55-67)-NH_2 (SEQ ID NO: 208) wherein the linker is of the formula G_{1-4} or $(CH_2)_{1-20}$.

The specification as originally filed does not provide adequate written description for a spacer with the formula $(CH_2)_{1-20}$. It is not expressly asserted in the specification. In the response filed 16 October 2006, Applicant indicates that support for such linker is found at pg 44, lines 20-23 and lines 26-28. However, the specification discloses that "[i]n some embodiments, $(CH_2)_n$ may for example be used as a linker between N- and C-terminal, where n is an integer and may for example be less than 20, 30, 40, 50, or 100" (pg 44, lines 26-28). The specification also teaches that the linker is a moiety such as NH_2-$(CH_2)_n$-COOH (n=0-20) (pg 17, lines 1-5; pg 62, lines 1-4). Thus, as indicated above, the specification as originally filed does not provide adequate written description for a spacer with the formula $(CH_2)_{1-20}$. (Please note that this issue could be overcome by amending claim 33 to recite, for example, "...wherein the LINKER is of the formula G_{1-4} (SEQ ID NO: 213) or $(CH_2)_n$, wherein n is less than 20".)

Conclusion

Claim 35 is allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Bridget E. Bunner whose telephone number is (571) 272-0881. The examiner can normally be reached on 8:30-4:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571) 272-0961. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

BEB
Art Unit 1647
29 December 2006

Bridget E. Bunner

BRIDGET BUNNER
PATENT EXAMINER